

**REMARKS**

**I. Introduction**

As an initial matter, applicants wish to thank Examiner Haghghatian and her supervisor, Examiner Padmanabhan for the courtesies extended by them during a February 21<sup>st</sup> telephonic interview. The amendments and remarks contained herein reflect the contents of that interview.

Receipt of a final Office Action dated November 30, 2005, is acknowledged. In the Action, claims 1-5 and 8-14 are rejected as allegedly anticipated by Wiedmann *et al.*, U.S. Patent No. 5,747,001 ("Wiedmann"), and claims 1-14 are rejected as allegedly obvious over Wiedmann, in view of Czekai et al., U.S. Patent No. 5,718,388 ("Czekai").

It is acknowledged that the foregoing amendments are submitted after final rejection. But because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance, entry thereof by the Examiner is respectfully requested.

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

**II. Status of the Claims**

In this response, applicants amended claim 1. Support for the amended claim can be found on page 18 of the specification. Upon entry of this amendment, claims 1-34 will be pending, and claims 1-14 will be under examination as claims 15-34 have been withdrawn. Upon allowance of claims 1-14, Applicants request rejoinder of method claims 15-30.

**III. Rejection of the Claims Under 35 U.S.C. § 102**

Claims 1-5 and 8-14 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wiedmann. Specifically, the claims are rejected because "Wiedmann is teaching filtration [*sic*] methods, such as simple filtration [*sic*], e.g.[,] sieving through a mesh filter or diafiltration using standard filtration [*sic*] equipment known in the art." Office Action at 3.

In addition, "Wiedmann also teaches particle sizes of less than 400 nm, less than 250 nm and less than 100 nm." *Id.* Applicants respectfully traverse this ground for rejection.

As previously stated, Wiedmann does not teach sterile filtered nanoparticulate active agent formulations, as required by the claimed invention. Specifically, the claimed invention recites a composition comprising nanoparticulate beclomethasone particles, nanoparticulate budesonide particles, or a combination thereof, having an effective particle size of less than about 150 nm, *wherein the nanoparticulate composition is sterile filtered.* See e.g. Claim 1.

Contrary to the Office's contention, conventional separation techniques such as simple filtration and sieving through a mesh screen are not analogous to sterile filtration. In fact, the membrane size of a sterile filter is substantially smaller than other filters and therefore, the process of sterile filtration as compared to other conventional separation techniques like simple filtration is not equivalent.

In fact, Wiedmann describes methods of making nanoparticulate beclomethasone dispersions by grinding with grinding media. See, column 6, line 29 - column 7, line 17 and column 8, line 38 - line 46. For both methods, Wiedmann describes a process for separating the grinding media from the milled particulate product "using conventional separation techniques, such as by filtration, sieving through a mesh screen, and the like." Col. 7 lines 18 - 22 and col. 8, lines 47 - 53. Wiedmann further describes the grinding media as having average sizes less than about 3 mm, preferably less than about 1 mm, and in the case of polymeric media, as small as 75 microns in diameter. See, col. 7, line 24 - col. 8, line 14, and col. 8, line 14. Thus, Wiedmann never discloses sterile filtering.

Indeed, the purpose of filtration in the context of Wiedmann is to separate large (75 micron - 3 mm) grinding media from a milled dispersion of nanoparticles. Based on Wiedmann, and for reasons of efficiency, one skilled in the art would use a filter or mesh screen with the largest possible pore size that could retain the grinding media (minimally tens of microns in diameter). One of skill in the art, however, understands a sterilizing filter to have a pore size of 0.2 microns or less. See, for example, the FDA/CDER Guidance on "

Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" dated August 2003, section IX. B.

Moreover, Wiedmann also makes reference to the use of dialysis and diafiltration for the purpose of removing salt formed during controlled precipitation. Col. 9, line 23. But in this case, the drug particles are not expected or required to pass through the dialysis membrane. Instead, dialysis (or diafiltration) is used to allow soluble salt ions to diffuse through a membrane into deionized water, thereby reducing the salt concentration in the precipitated dispersion. In contrast, sterile filtration requires that the drug particle to pass through the sterilizing filter membrane. Thus, the ability to diafilter or dialyze a nanoparticulate dispersion does not in any way imply or indicate that the compositions of the present invention can be sterile filtered. Thus, since Wiedmann does not teach each and every element of the claimed invention, claims 1-14 are not anticipated by the cited art.

While the Office states that “the instant claims are drawn to a composition, and ‘sterile filtration’ is a method step” (Office Action at 4), a composition that has been sterile filtered is different from a composition that is not sterile filtered. Although the act of sterile filtering is a step in a method, a composition that has been sterile filtered is a characteristic of that composition. Nevertheless, for clarity’s sake, and in the interest of expediting prosecution, applicants amended claim 1 to recite a “sterile” nanoparticulate composition and incorporate the pore sizes of the sterile filter into the claim. Support for this amendment can be found throughout the specification and on page 18, paragraph 4 of the originally filed application.

#### **IV. Rejection of the Claims Under 35 U.S.C. § 103**

Claims 1-14 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Wiedmann in view of Czekai. In particular, the claims are rejected because “Wiedmann DOES disclose beclomethasone with tyloxapol on its surface, particle size of less than 250 or 100 nm and teaches filtration [*sic*].” Office Action at 3. In addition, “Czekai was employed for its teachings on particles smaller than 80 or 50 nm.” Office Action at 4. Applicants respectfully traverse this ground for rejection.

To establish a *prima facie* case of obviousness, there must be: (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) when combined, a teaching or suggestion of all the claim limitations in the prior art references. *See* MPEP §2143 (Aug. 2001). “Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Wiedmann teaches compositions comprising: (1) nanoparticulate beclomethasone particles, and (2) a surface modifier selected from an exhaustive list of exemplary surface modifiers (*see e.g.*, col. 3, line 30, through col. 5, line 65, of Wiedmann). Wiedmann, however, does not teach that it is not possible to make sterile-filtered dispersions of beclomethasone or budesonide with stabilizers other than tyloxapol. In fact, it is Applicants who surprisingly and unexpectedly discovered that nanoparticulate beclomethasone or budesonide particles having tyloxapol as a surface modifier can be prepared at a very small particle size allowing for sterile filtering. Applicants surprisingly discovered that other corticosteroids having tyloxapol as a surface stabilizer cannot be sterile filtered.

This deficiency is not cured by the teachings in Czekai since Czekai does not disclose sterile filtering or that when beclomethasone and budesonide have one or more non-tyloxapol surface stabilizers, the compositions cannot be sterile filtered. Accordingly, the combination of Wiedmann and Czekai would not teach each and every element of the claimed invention.

Therefore, for at least these reasons, the present invention is not obvious in view of Wiedmann and Czekai.

## CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments. The present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

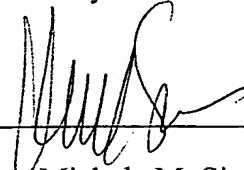
The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

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Respectfully submitted,

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